General

Guideline Title

Diagnosis and management of epilepsy in adults. A national clinical guideline.

Bibliographic Source(s)

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2015 May. 94 p. (SIGN publication; no. 143). [453 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version:

- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 49 p. (SIGN publication; no. 70). [295 references]
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. Update to printed guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2004 Jun 7. 3 p. [1 reference]

Any amendments to the guideline will be noted on the Scottish Intercollegiate Guidelines Network (SIGN) Web site .

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- December 14, 2016 – General anesthetic and sedation drugs : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.
- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that

depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.

Recommendations

Major Recommendations

Note from the Scottish Intercollegiate Guidelines Network (SIGN) and National Guideline Clearinghouse (NGC): In addition to these evidence-based recommendations, the guideline development group also identifies good practice points in the full-text guideline document.

The grades of recommendations (A-D) and levels of evidence (1++, 1+, 1-, 2++, 2+, 2-, 3, 4) are defined at the end of the "Major Recommendations" field.

Diagnosis

Who Should Make the Diagnosis of Epilepsy?

C - The diagnosis of epilepsy should be made by an epilepsy specialist.

Definition and Classification

The Relevance of Classification in Clinical Practice

C - The seizure type(s) and epilepsy syndrome should be identified.

C - The distinction should be made between a focal epilepsy and a genetic generalised epilepsy.

Clinical Factors and Diagnosis

Polysomnography

C - A clear history from the patient and an eyewitness to the attack give the most important diagnostic information, and should be the mainstay of diagnosis.

Use of Electroencephalography (EEG) in the Diagnosis and Classification of Epilepsy

C - EEG is not routinely indicated and cannot exclude a diagnosis of epilepsy.

C - EEG should be used to support the classification of epileptic seizures and epilepsy syndromes when there is clinical doubt.

C - EEG should be performed in young people with generalised seizures to aid classification and to detect a photoparoxysmal response.

B - Short-term video-EEG, preferably with suggestion, should be available for the investigation and diagnosis of suspected epilepsy and non-epileptic attack disorder.

C - Inpatient video-EEG monitoring and other specialist investigations (including polysomnography with full EEG montages) should be available for patients who present diagnostic difficulties.

Brain Imaging

Computed Tomography

C - Magnetic resonance imaging (MRI) is the modality of choice for brain imaging in patients with epilepsy.

C - Brain imaging is not routinely required when there is a confident diagnosis of a genetic generalised epilepsy.

D - Computed tomography (CT) has a role in the urgent assessment of seizures, or when MRI is contraindicated.

Treatment

When to Start Antiepileptic Treatment

Single Seizures

B - The decision to start antiepileptic drugs (AEDs) should be made by the patient and an epilepsy specialist.

AEDs should be offered after a first tonic-clonic seizure if:

- B - The patient has had previous myoclonic, absence or partial seizures
- B - The EEG shows unequivocal epileptic discharges
- B - The patient has a structural cerebral disorder
- D - The patient considers the risk of recurrence unacceptable

Antiepileptic Drug Monotherapy

Choice of Formulation

A - In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives.

A - In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug.

- A - Where sodium valproate is poorly tolerated or contraindicated, lamotrigine and topiramate are suitable alternatives.
- D -In women of childbearing age, levetiracetam or lamotrigine may be a reasonable alternative.

C - Routine switching between different manufacturers of antiepileptic drugs should be avoided.

Management of Drug-resistant Epilepsy

Drug-resistant Generalised or Unclassified Epilepsy

C - Failure to respond to appropriate antiepileptic drugs should prompt a review of the diagnosis of epilepsy and adherence to medication.

D - Combination therapy should be considered when treatment with two first-line antiepileptic drugs has failed or when improved control occurs during the process of phased substitution.

A - Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy.

A - Lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy.

B - The choice of drugs in combination should be matched to the patient's seizure type(s) and should, where possible, be limited to two or at most three antiepileptic drugs.

Antiepileptic Drug Blood Levels

D - Routine monitoring of antiepileptic drug concentrations is not indicated. Measurement can sometimes be useful in the following circumstances:

- Adjustment of phenytoin dose
- Assessment of adherence
- Assessment of toxicity
- Situations where drug metabolism is likely to change, e.g., pregnancy
- Otherwise unexplained loss of seizure control

Management of Provoked Seizures

B - Following an acute brain insult or neurosurgery, long-term prophylactic antiepileptic drug treatment is not indicated.

C - Following an acute brain insult, antiepileptic drugs used to treat the provoked seizures should be withdrawn (unless unprovoked seizures occur later).

D - Antiepileptic drug treatment is not indicated for concussive convulsions.

Antiepileptic Drug Adverse Effects

Chronic Systemic Adverse Effects

C - Patients should be warned of common potential adverse effects and given clear instructions to seek medical attention urgently for symptoms including rash, bruising or somnolence with vomiting especially in the first weeks of treatment.

D - Liver function and full blood count should not be monitored routinely.

Bone Health

C - Patients taking antiepileptic drugs should receive dietary and other lifestyle advice to minimise the risk of osteoporosis.

Psychiatric and Behavioural Adverse Effects of Antiepileptic Drugs

B - The potential negative psychotropic effects of antiepileptic drugs should be borne in mind when deciding on the most appropriate antiepileptic drug treatment for an individual patient.

Antiepileptic Drug Withdrawal

A - Prognostic index indicators can be used to give an estimate of the risks of seizure recurrence following antiepileptic drug withdrawal.

Surgical Referral

B - Referral for assessment for neurosurgical treatment should be considered if the epilepsy is drug resistant.

D - Assessment as to suitability for a potentially curative resective procedure should be made before consideration of palliative procedures such as vagus nerve stimulation (VNS).

Vagus Nerve Stimulation

C - VNS may be considered in adult patients who have been found to be unsuitable for resective surgery.

Management of Prolonged Seizures Including *Status Epilepticus*

D - EEG should be used for confirming diagnosis of and monitoring treatment effect in patients with *status epilepticus*. EEG should be available as an emergency intervention for all patients with treated or suspected *status epilepticus*.

Immediate Measures

B - Patients with prolonged tonic-clonic seizures that have lasted five minutes or more should be given:

- Midazolam 10 mg buccally or intranasally, or
- Lorazepam 4 mg intravenously (IV) if midazolam is unavailable, or
- Diazepam 10 mg IV or rectally if midazolam and lorazepam are unavailable

In-Hospital Treatment (Following Failure of Initial Benzodiazepine)

B - Administer a repeat dose of benzodiazepine in hospital after 10 minutes if there is no response.

D - Within 30 minutes, if seizures continue:

- Give sodium valproate 20–30 mg/kg IV 40 mg/min, or phenytoin 18 mg/kg IV 50 mg/min with ECG monitoring. Rates of phenytoin infusion may need to be reduced if hypotension or arrhythmia occur in older people or where there is renal/hepatic impairment.

Seizures Persisting Longer Than 30 Minutes

D - If *status* persists, then within 60 minutes:

- Admit the patient to an intensive treatment unit and administer general anaesthesia
- Refer for specialist advice

D - EEG should be used to determine response to treatment.

Non-convulsive Status Epilepticus

D - EEG should be used for diagnosing and monitoring treatment response in patients with nonconvulsive *status epilepticus*.

Patients with Recurrent Prolonged or Serial Seizures in the Community

B - Patients with recurrent prolonged or serial seizures in the community should be initially managed by carers who should give midazolam 10 mg buccally or intranasally, or diazepam 10–20 mg rectally according to an agreed administration protocol.

D - All carers of patients with epilepsy who may require buccal midazolam or rectal diazepam should receive recognised training in its administration.

D - Where a care plan is required, it should be drawn up in consultation with the general practitioner (GP) and/or specialist service, used by everyone working with the individual patient, and reviewed at regular intervals.

Management of Older People with Epilepsy

Antiepileptic Drug Treatment

B - Lamotrigine or possibly levetiracetam should be considered when starting antiepileptic drug treatment in older people with focal-onset seizures.

C - Gabapentin is an alternative mono- or adjunctive therapy option in older people with epilepsy.

Management of People with Learning Disability and Epilepsy

D - People with learning disability should be treated with the same range of antiepileptic drugs as the general population.

Epilepsy and Women's Health

Contraception

Lamotrigine

C - To minimise the risk of contraceptive failure, a woman using any combined hormonal contraception, or a combined oral contraceptive pill, or a progesterone-only pill should be prescribed an antiepileptic drug that does not induce hepatic enzymes.

D - For women receiving hepatic enzyme-inducing antiepileptic drugs:

- The levonorgestrel intrauterine system may be used without restriction.
- Depot injections of progestogen may be used without restriction and with no alteration to the normal dosing/replacement interval.
- Progestogen-only oral contraceptives are not recommended.
- Progestogen implants (levonorgestrel and etonogestrel) are not recommended.
- If there is no alternative to a combined oral contraceptive pill (COCP), the COCP should contain at least 50 micrograms daily of oestrogen; if the COCP contains less oestrogen, the woman should be warned that the efficacy is reduced and additional barrier methods should be used.
- If breakthrough bleeding occurs with a COCP containing 50 micrograms of oestrogen, the COCP dose should be increased to a maximum of 70 micrograms and 'tricycling' should be considered.
- If the antiepileptic drug is withdrawn, it is important to note that enzyme induction persists for up to four weeks. Contraceptive cover should be ensured during this time.

D - Women with epilepsy receiving lamotrigine:

- Can use progestogen-only contraceptives without restriction. These women should be made aware of signs and symptoms of lamotrigine toxicity, and have the lamotrigine dose reduced if these occur.
- And combined hormonal contraceptives should be counselled about the reduction in circulating lamotrigine concentrations and the potential for, and consequences of, increased seizure activity. The healthcare professional should also discuss the possibility of increasing the lamotrigine dose with the patient.
- And combined hormonal contraceptives should be warned about signs and symptoms of lamotrigine toxicity if the contraceptive is withdrawn. A reduction in lamotrigine dosing may be necessary at this time.

Emergency Contraception

D - Women with epilepsy who are not taking antiepileptic drugs, or who are taking non-enzyme inducing antiepileptic drugs, including lamotrigine, can use emergency contraception as for the general population.

D - Women with epilepsy who require emergency contraception while using enzyme-inducing antiepileptic drugs, or who have stopped taking these within the last 28 days:

- Should be prescribed a single dose of levonorgestrel 3 mg (as opposed to 1.5 mg), ideally as soon as possible, and within 72 hours of unprotected intercourse
- Should not be offered ulipristal acetate (ellaOne®) because of a risk of reduced efficacy
- May be offered insertion of a non-hormonal intrauterine device within 5 days of intercourse as an alternative option

Preconceptual Counseling

Women with epilepsy should:

- B - Receive prepregnancy counselling at the time of diagnosis and at regular intervals during their management, especially if they are taking antiepileptic drug treatment
- D - Be reassured that most will have a normal pregnancy and delivery
- C - Have their diagnosis and treatment, if appropriate, reviewed by specialist services before conception; a concerted effort should be made to optimise seizure control and rationalise antiepileptic drug therapy prior to conception
- D - Be well informed about pregnancy and epilepsy-related issues, including smoking cessation, before conception

Folic Acid

C - Women with epilepsy trying to conceive or who present in the first trimester should be advised to take folic acid during this time to reduce the risk of major congenital malformations.

D - Women receiving sodium valproate should be advised that folic acid supplementation may reduce the rate of spontaneous miscarriage.

Folic acid dosing:

- 400 micrograms daily for -
  - A - Women with epilepsy not receiving antiepileptic drug treatment
- 5 mg daily for -
  - D - Women with epilepsy receiving antiepileptic drug treatment
  - A - Women with epilepsy not on antiepileptic drug treatment, but with a family history of or a previous child with a neural tube defect
  - A - Women with epilepsy not on antiepileptic drug treatment, but with a body mass index (BMI) >30.

Pregnancy

Seizure Control During Pregnancy

D - As good seizure control during pregnancy is more likely in women whose seizures are controlled prior to becoming pregnant an effort should be made to optimise seizure control prior to pregnancy (particularly for generalised tonic-clonic seizures).

AED Doses and Blood Level Monitoring During Pregnancy

D - In pregnancy, dosing adjustment for the majority of antiepileptic drugs (with the exception of lamotrigine and levetiracetam) should only be considered if there is a change in seizure frequency or if toxicity is suspected.

D - Healthcare professionals should be aware that the dose of lamotrigine may need to be increased during pregnancy. To avoid postpartum neurotoxicity, the lamotrigine dose should be reduced early in the puerperium.

Pregnancy Complications

D - Pregnant women with epilepsy receiving hepatic enzyme-inducing antiepileptic drugs who require antenatal corticosteroids for the prevention of neonatal respiratory morbidity, should receive double the standard dose of betamethasone/dexamethasone (48 mg over 12–24 hours).

D - All infants of women with epilepsy should be offered vitamin K_1, 1 mg intramuscularly at birth, unless there are contraindications.

D - If there are additional risk factors for haemorrhagic disease of the newborn (for example maternal liver disease, anticipated premature delivery)

consideration should be given to the maternal administration of oral vitamin K_1 (phytomenadione 10 mg daily) in the third trimester of pregnancy.

Labour and Birth

D - The usual oral antiepileptic drug should be continued during labour and in the postnatal period. Every effort should be made to ensure that no doses are missed. In women with epilepsy who are unable to tolerate oral medication, the antiepileptic drug can be given by other routes.

Seizures in Labour

D - Intrapartum generalised tonic-clonic seizures that are not due to eclampsia should be terminated as soon as possible.

D - If the seizure persists, this should be managed as for *status epilepticus*.

Fetal, Neonatal and Childhood Outcomes

Risks to the Fetus from Maternal Seizures

D - Pregnant women with epilepsy should be made aware of the risks of uncontrolled seizures both to themselves and to their developing fetus.

Risks to the Fetus Associated with Antiepileptic Drug Monotherapy

D - Women with epilepsy should be informed that sodium valproate is associated with a higher rate of teratogenicity compared to other antiepileptic drugs.

Risks to the Fetus Associated with Antiepileptic Drug Polytherapy

D - Women with epilepsy should be informed that antiepileptic drug polytherapy regimens including sodium valproate are associated with higher rates of congenital malformations compared to regimens not including sodium valproate.

Perinatal Outcomes

C - Women with epilepsy should be reassured that antiepileptic drugs do not increase the risk of spontaneous miscarriage and stillbirth.

Advice about Breastfeeding

D - Parents should be made aware of signs of toxicity in infants of breastfeeding women taking antiepileptic drugs. The possibility of sedation should be considered in infants of mothers taking high dose antiepileptic drugs, polytherapy, or regimens including primidone, levetiracetam, gabapentin, lamotrigine and topiramate.

Menopause and Epilepsy

D - Women should be aware that their seizure pattern may change around the menopause.

D - Hormone replacement therapy should be prescribed for the same indications as in women who do not have epilepsy.

Psychiatric Comorbidity

Screening

Future Research

D - Screening for depression and suicidality should be considered in all patients with epilepsy.

D - The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Hospital Anxiety and Depression Scale Depression subscale (HADS-D), Beck's Depression Inventory (BDI-II) or Patient Health Questionnaire 2 (PHQ-2) can all be used to screen for depression in adults with depression and epilepsy. The NDDI-E may be superior for detecting severe depression and suicidal ideation.

Treatment Options

Psychotropic Medication

D - Treatment with antidepressants should be considered in patients with epilepsy and comorbid depression.

Mortality

Sudden Unexpected Death in Epilepsy (SUDEP)

Risk Factors

B - Healthcare professionals and patients should aim for complete seizure freedom to reduce the risk of SUDEP.

D - Adherence to the prescribed antiepileptic drug regime should be strongly encouraged and the patient asked to report any adverse effects that might compromise adherence in order to reduce the risk of increased mortality and morbidity.

Counselling Patients About the Risks of SUDEP

D - Counselling about the risks of SUDEP should be considered for patients with epilepsy at an appropriate time for the patient and by an appropriate healthcare professional (consultant neurologist, physician with an interest in epilepsy, specialist registrar, or epilepsy nurse specialist).

Models of Care

Models of Primary Care for Epilepsy

Regular Structured Review

D - A structured management system for patients with epilepsy should be established in primary care. As with other chronic diseases, an annual review is desirable.

D - The annual review should be facilitated by specialist epilepsy nurses, linking primary care to the hospital system (shared care).

D - The shared care management system adopted should seek to:

- Identify all patients with epilepsy, register/record basic demographic data, validate the classification of seizures and syndromes
- Make the provisional diagnosis in new patients, provide appropriate information and refer the patient to a specialist centre
- Monitor seizures, aiming to improve control by adjustment of medication or re-referral to hospital services
- Minimise the adverse effects of medications and their interactions
- Facilitate structured withdrawal from medication where appropriate, and if agreed by the patient
- Introduce non-clinical interventions, and disseminate information to help improve the quality of life for patients with epilepsy
- Address specific women's issues
- Address the needs of patients with learning disabilities

D - Healthcare professionals who carry out structured primary-care reviews for patients with epilepsy should have attended an epilepsy training course in the past five years or be able to demonstrate equivalent experience from continuing professional development.

D - Patients presenting to primary care with suspected first seizure or new epilepsy should be referred to an epilepsy specialist and asked to take an eyewitness or eyewitness contact details if available, to the appointment.

D - Patients with treatment-resistant epilepsy should have the opportunity to receive shared care to enable accurate classification and tailored management of their seizures.

D - Women of childbearing potential who are taking antiepileptic drugs should receive information about contraception, conception and pregnancy at their regular structured review in primary care and should have the opportunity to be referred to secondary care to have their diagnosis and treatment reviewed by specialist services before conception.

D - Patients referred following a suspected first seizure or new epilepsy should be advised not to drive until they have seen an epilepsy specialist.

D - Patients with epilepsy who hold a driving license and who continue to have seizures should be made aware of current Driver and Vehicle Licensing Agency (DVLA) regulations.

Role of the Epilepsy Specialist Nurse

D - Each epilepsy team should include epilepsy specialist nurses.

Definitions

Levels of Evidence

1++: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++: High-quality systematic reviews of case-control or cohort studies

High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Grades of Recommendation

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A: At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D: Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Clinical Algorithm(s)

An algorithm titled "Proposed Management Approach for Women and Teenage Girls with Epilepsy Treated with Antiepileptic Drugs " is provided in the original guideline document.

Scope

Disease/Condition(s)

- Epilepsy
- *Status epilepticus*

Guideline Category

Counseling

Diagnosis

Management

Treatment

Clinical Specialty

Emergency Medicine

Family Practice

Internal Medicine

Neurology

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Social Workers

Guideline Objective(s)

To provide recommendations based on current evidence for best practice in the diagnosis and management of epilepsy in adults

Target Population

Adult patients with epilepsy or *status epilepticus*

Note: This guideline does not include patients with a non-epileptic attack disorder.

Interventions and Practices Considered

Diagnosis

1. Diagnosis of epilepsy made by epilepsy specialist
2. Identification and classification of seizure type
3. Patient history
4. Electroencephalography (EEG), including video-EEG
5. Brain imaging (magnetic resonance imaging [MRI] and computed tomography [CT] scanning)

Treatment/Management

1. Antiepileptic drug (AED) monotherapy (carbamazepine, sodium valproate, lamotrigine, topiramate, oxcarbazepine, and levetiracetam)
2. Combination AED therapy
3. AED blood level monitoring

4. Management of provoked seizures
5. Monitoring of AED adverse effects and offering patients advice and counsel concerning AED adverse effects
6. Referral for assessment for neurosurgical treatment
7. Management of prolonged seizures including *status epilepticus* (initial benzodiazepine and in-hospital treatment when necessary)
8. Management of non-convulsive *status epilepticus*
9. Management of recurrent prolonged or serial seizure episodes
10. Management considerations for older people and people with learning disabilities
11. Management of psychiatric comorbidities (depression and suicide)
12. Reduction of the risk of sudden unexpected death in epilepsy (SUDEP)
13. Structured management systems

Women's Health Issues (Contraception, Pregnancy, and Menopause Management)

1. Minimization of contraceptive failure risk (antiepileptic drugs that do not induce hepatic enzymes)
2. Considerations for women receiving hepatic enzyme-inducing antiepileptic drugs and lamotrigine
3. Emergency contraception
4. Preconceptual counselling, including advice on folic acid intake
5. Seizure control during pregnancy
6. AED and blood level monitoring during pregnancy
7. Offering vitamin K_1 to infants of women with epilepsy
8. Management of seizure in labour
9. Advising women on risks to the fetus associated with AED therapy and childhood outcomes
10. Providing advice about breastfeeding and AED toxicity
11. Management of menopause (hormone replacement therapy)

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Seizure frequency
- Seizure severity scales
- Adverse effects of treatments
- Quality of life
- Seizure control
- Neurological disability
- Mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review

The evidence base for this guideline was synthesised in accordance with Scottish Intercollegiate Guidelines Network (SIGN) methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, EMBASE, CINAHL, PsycINFO and the Cochrane Library. The year range covered was 2001–2013. Internet searches were carried out on various Web sites including the US National Guideline Clearinghouse (NGC). The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence. Please refer to the search strategy

document for further information on the search strategy, including search terms used (see the "Availability of Companion Documents" field).

Literature Search for Patient Issues

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to the diagnosis and management of epilepsy in adults. Databases searched include Medline, EMBASE, CINAHL and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

Number of Source Documents

See the search strategy document (see the "Availability of Companion Documents" field) for results of the literature search process.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

1++: High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++: High-quality systematic reviews of case-control or cohort studies

High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

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2-: Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Once papers have been selected as potential sources of evidence, the methodology used in each study is assessed to ensure its validity. The result of this assessment will affect the level of evidence allocated to the paper, which will in turn influence the grade of recommendation that it supports.

The methodological assessment is based on a number of key questions that focus on those aspects of the study design that research has shown to have a significant influence on the validity of the results reported and conclusions drawn. These key questions differ between study types, and a range of checklists is used to bring a degree of consistency to the assessment process. Scottish Intercollegiate Guidelines Network (SIGN) has based its assessments on the MERGE (Method for Evaluating Research and Guideline Evidence) checklists developed by the New South Wales Department of Health, which have been subjected to wide consultation and evaluation. These checklists were subjected to detailed evaluation and adaptation to meet SIGN's requirements for a balance between methodological rigour and practicality of use.

The assessment process inevitably involves a degree of subjective judgement. The extent to which a study meets a particular criterion - e.g., an

acceptable level of loss to follow up - and, more importantly, the likely impact of this on the reported results from the study will depend on the clinical context. To minimise any potential bias resulting from this, each study must be evaluated independently by at least two group members. Any differences in assessment should then be discussed by the full group. Where differences cannot be resolved, an independent reviewer or an experienced member of SIGN Executive staff will arbitrate to reach an agreed quality assessment.

Evidence Tables

A completed evidence table based on an internally conducted systematic review of the literature will be provided for all questions. These will either update existing reviews or provide a review of all relevant literature. Each evidence table will include methodological evaluation of and data from each individual study relevant to a specific key question. Study results will be reported on a per outcome basis wherever possible. An example of a completed evidence table records appears in Figure 5-1 of the SIGN Handbook. Additional details can be found in the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [Scotland]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50]), available from the SIGN Web site .

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Synthesising the Evidence

Guideline recommendations are graded to differentiate between those based on strong evidence and those based on weak evidence. This judgement is made on the basis of an (objective) assessment of the design and quality of each study and a (perhaps more subjective) judgement on the consistency, clinical relevance and external validity of the whole body of evidence. The aim is to produce a recommendation that is evidence-based, but which is relevant to the way in which health care is delivered in Scotland and is therefore implementable.

It is important to emphasise that the grading does not relate to the importance of the recommendation, but to the strength of the supporting evidence and, in particular, to the predictive power of the study designs from which that data was obtained. Thus, the grading assigned to a recommendation indicates to users the likelihood that, if that recommendation is implemented, the predicted outcome will be achieved.

Considered Judgement

It is rare for the evidence to show clearly and unambiguously what course of action should be recommended for any given question. Consequently, it is not always clear to those who were not involved in the decision making process how guideline developers were able to arrive at their recommendations, given the evidence they had to base them on. In order to address this problem, the Scottish Intercollegiate Guidelines Network (SIGN) has introduced the concept of considered judgement.

Under the heading of considered judgement, guideline development groups summarise their view of the total body of evidence covered by each evidence table.

Each guideline group considers the following factors:

- Quantity, quality, and consistency of evidence
- External validity (generalisability) of studies
- Directness of application to the target population for the guideline
- Any evidence of potential harms associated with implementation of a recommendation
- Clinical impact (i.e., the extent of the impact on the target patient population, and the resources needed to treat them in accordance with the recommendation)
- Whether, and to what extent, any equality groups may be particularly advantaged or disadvantaged by the recommendations made
- Implementability (i.e., how practical it would be for the National Health Service (NHS) Scotland to implement the recommendation.)

Then the group is asked to summarise its view on all of these issues, both the quality of the evidence and its potential impact, before making a recommendation. This summary should be succinct, and taken together with its views of the level of evidence represent the first draft of the text that will appear in the guideline immediately before a recommendation.

Additional detail about SIGN's process for formulating guideline recommendations is provided in Section 7 of the companion document titled

"SIGN 50: A Guideline Developers' Handbook." (Edinburgh [Scotland]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50]), available from the SIGN Web site .

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A: At least one meta-analysis, systematic review, or randomised controlled trials (RCT) rated as 1++ and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rate as 2++

D: Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Consultation and Peer Review

National Open Meeting

A national open meeting is the main consultative phase of Scottish Intercollegiate Guidelines Network (SIGN) guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on February 3, 2014 and was attended by 105 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN Web site for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

Specialist Review

This guideline was also reviewed in draft form by independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of

interest and further details of these are available on request from the SIGN Executive.

SIGN Editorial Group

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline can be found in Section 13.3.3 of the original guideline document.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Patients with seizures provoked by alcohol or substance misuse may benefit from referral to addiction services and other support agencies
- For each individual the potential benefits of improved seizure control, quality of life and possible reduction in antiepileptic medication need to be balanced against the risks of the surgical procedure.
- Women with epilepsy of childbearing potential who receive advice about contraception and pregnancy as well as information about epilepsy management are likely to have more reliable contraception, better health during pregnancy and improved pregnancy outcomes.

Potential Harms

- Antiepileptic drug (AED) adverse effects are common and a major cause of drug failure. Most are mild but a minority can be life threatening. Accurate data on prevalence of adverse drug reactions (ADRs) with long term AED treatment is scarce; almost all reports refer to short-term clinical trials and, as experience with vigabatrin and visual-field defects has shown, long-term surveillance is needed to identify all ADRs. Older people are more sensitive to AED adverse effects. See section 4.6 in original guideline document for details regarding adverse effects, including dose-related adverse effects, idiosyncratic ADRs, chronic systemic adverse effects, risks to bone health (e.g., fractures and osteoporosis), and psychiatric and behavioural adverse effects.
- Evidence of the risks of seizure recurrence after discontinuation of AEDs was provided by a large, multicentre, randomised, prospective trial of continued antiepileptic treatment versus slow withdrawal in adults and children with epilepsy who had been seizure free for at least two years. AED withdrawal was associated with an increased risk of seizure recurrence, which was influenced by the duration of seizure freedom, the history of seizure types, the occurrence of one or more seizures after the start of the treatment and whether one, or more than one, AED was being taken.
- AED treatment can be complicated by the frequent coexistence of epilepsy and dementia, comedication, and the increased likelihood of dose-related and idiosyncratic adverse effects. In this population, the use of carbamazepine is limited by its enzyme inducing properties, implicating the AED in a range of pharmacokinetic interactions. The drug also has a propensity to cause hyponatraemia, particularly in patients taking diuretics.
- Women with epilepsy are more likely than women without epilepsy to give birth to children with congenital malformations (CMs). Untreated epilepsy does not appear to be associated with an increased risk of CM, but major and minor fetal malformations occur more commonly in infants exposed to AEDs during pregnancy. The reported rates of major CMs associated with different AED monotherapies vary from study to study and different methodological approaches make comparison between studies difficult. Rates are, however, consistently higher for sodium valproate than for other AEDs (see Table 4 in the original guideline document).
- Following delivery, physiological changes associated with pregnancy gradually remit and blood levels of AEDs may rise. If AED dosing was increased in pregnancy, this may lead to toxicity postpartum and dosing may need to be reduced at this time.
- Adverse outcomes that have been linked to AEDs in pregnancy include childhood verbal language impairment associated with fetal exposure to sodium valproate, impaired neurodevelopment in infants exposed to sodium valproate or carbamazepine but not lamotrigine, and autism spectrum disorder and childhood autism in children exposed to sodium valproate prenatally. There is, however, insufficient

evidence to make recommendations about treatment with any specific AED or combination of AEDs.

- Although AEDs pass into breast milk at varying levels there is no consistent evidence to show accumulation of any AED in breastfed newborn of women with epilepsy. Data suggest probable penetration into breast milk of primidone and levetiracetam in amounts that may be clinically important, possible penetration of gabapentin, lamotrigine and topiramate, and probably no penetration, in clinically important amounts, of sodium valproate, phenobarbital, phenytoin and carbamazepine. Breastfeeding and subsequent weaning usually allow for a gradual withdrawal with usually no adverse sequelae for the infant. Accumulation of AEDs may occur due to immature mechanisms for drug elimination and, therefore, close monitoring is recommended, particularly if the baby is preterm, jaundiced, or if the mother started taking AEDs late in pregnancy or after delivery. There may also be a risk of toxicity in the breastfed infant if the mother is on a high dose of AEDs or polytherapy. Parents should be made aware of signs of toxicity in the infant and encouraged to seek medical advice if these occur.
- Data regarding hormone replacement therapy (HRT) and seizures are conflicting. HRT may improve seizure control in those who previously experienced catamenial epilepsy (seizures with menstruation) but could be associated with increased seizure frequency in others. One small study found HRT containing the combination of conjugated equine oestrogens and medroxyprogesterone acetate was associated with worsening seizures and a reduction in lamotrigine concentrations. Enzyme-inducing AEDs (see Table 3 in the original guideline document) reduce the efficacy of standard doses of HRT.
- Adverse effects reported with vagus nerve stimulation (VNS) in one review were found to differ from those for AEDs and included hoarseness, cough, pain, paresthesias and dyspnea, although these appeared to be reasonably well tolerated as dropouts were rare.
- Low-dose topiramate (25 mg to 50 mg daily) may be useful as mono- or adjunctive therapy in older people, although adverse effects including somnolence, dizziness, headache and cognitive-related events have been reported.

Contraindications

Contraindications

Progesterone-only oral contraception, which is often the contraceptive method of choice in women who are breastfeeding, is contraindicated postpartum in women with epilepsy taking hepatic enzyme-inducing antiepileptic drugs as these increase progesterone metabolism.

Qualifying Statements

Qualifying Statements

- This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.
- Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.
  Medicines may be prescribed off label in the following circumstances:

  - For an indication not specified within the marketing authorization
  - For administration via a different route
  - For administration of a different dose
  - For a different patient population

  An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

  Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

  "Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional

responsibility and potential liability."

The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

- Be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- Be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- Record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- Take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory body and the prescribing practices of their employers.

Implementation of the Guideline

Description of Implementation Strategy

Implementation of national clinical guidelines is the responsibility of each National Health Service (NHS) board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by the Scottish Intercollegiate Guidelines Network (SIGN).

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2015 May. 94 p. (SIGN publication; no. 143). [453 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2003 Apr (revised 2015 May)

Guideline Developer(s)

Scottish Intercollegiate Guidelines Network - National Government Agency [Non-U.S.]

Source(s) of Funding

Scottish Executive Health Department

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

Guideline Development Group: Professor Martin Brodie (*Chair*), Clinical and Research Director, Epilepsy Unit, Western Infirmary, Glasgow; Ms Beatrice Cant, Programme Manager, SIGN; Dr Anne Coker, General Practitioner, Ninewells Hospital, Dundee; Dr Sue Copstick, Consultant Clinical Neuropsychologist, Southern General Hospital, Glasgow; Ms Alison Corp, Learning Disability Epilepsy Specialist Nurse, Learning Disability Tier 4 Services, Glasgow; Dr Chris Derry, Consultant Neurologist, Western General Hospital, Edinburgh; Dr Susan Duncan, Lead, South East Scotland Epilepsy Service and Consultant Neurologist, University of Edinburgh and Western General Hospital, Edinburgh; Dr Andrew Elder, Consultant in Acute Elderly Medicine, Western General Hospital, Edinburgh; Mr Gerard Gahagan, Head of Clinical Services, Scottish Epilepsy Centre, Quarriers, Bridge of Weir; Ms Irene Hamill, Epilepsy Nurse Specialist, Southern General Hospital, Glasgow; Dr Jean Hannah, Clinical Director, Nursing Homes Medical Practice, Glasgow; Mrs Heather Harrison, Prescribing Support Pharmacist, Glasgow; Ms Zareen Iqbal, Development Co-ordinator, Ethnic Minorities Project, Epilepsy Connections, Glasgow; Dr Bethany Jones, Consultant Neurologist, Raigmore Hospital, Inverness; Dr John Paul Leach, Consultant Neurologist, Southern General Hospital, Glasgow; Ms Yvonne Leavy, Epilepsy Nurse Specialist, Western General Hospital, Edinburgh; Mr Stuart Macgee, Patient representative, Kilmarnock; Dr Tony Nicoll, Consultant Obstetrician and Honorary Senior Lecturer, Ninewells Hospital, Dundee; Dr Maria Oto, Consultant Neuropsychiatrist, Scottish Epilepsy Centre, Glasgow; Dr Carolyn Sleith, Evidence and Information Scientist, SIGN; Dr Linda Stephen, Associate Specialist, Epilepsy Unit, Western Infirmary, Glasgow; Dr Jane Stuart, Associate Specialist, Learning Disability Psychiatry, Edinburgh; Ms Gayle Weir, Epilepsy Fieldworker, Epilepsy Connections, Glasgow; Dr Kathleen White, Consultant Neurologist, Ninewells Hospital, Dundee; Dr Margo Whiteford, Consultant Clinical Geneticist, Southern General Hospital, Glasgow; Ms Lesslie Young Chief Executive, Epilepsy Scotland, Glasgow

Financial Disclosures/Conflicts of Interest

All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version:

- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Apr. 49 p. (SIGN publication; no. 70). [295 references]
- Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. Update to printed guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2004 Jun 7. 3 p. [1 reference]

Any amendments to the guideline will be noted on the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

Availability of Companion Documents

The following are available:

- Diagnosis and management of epilepsy in adults. Quick reference guide. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2015 May. 11 p. Available from the Scottish Intercollegiate Guidelines Network (SIGN) Web site.
- Diagnosis and management of epilepsy in adults. Search strategies. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2015 May. 9 p. Available from the SIGN Web site.
- SIGN 50: a guideline developers' handbook. Edinburgh (UK): Scottish Intercollegiate Guidelines Network. (SIGN publication; no. 50). 2014 Oct. 62 p. Available from the SIGN Web site.

Executive summaries of SIGN guidelines are available for mobile devices through the guidelines app on the SIGN Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on November 20, 2003. The information was verified by the guideline developer on January 16, 2004. This summary was updated by ECRI on September 28, 2004. The information was verified by the guideline developer on January 26, 2005. This summary was updated by ECRI on April 21, 2005 following the release of a public health advisory from the U.S. Food and Drug Administration (FDA) regarding Trileptal (oxcarbazepine). This summary was updated by ECRI on November 16, 2006 following the FDA advisory on Lamictal (lamotrigine). This summary was updated by ECRI Institute on October 2, 2007 following the FDA advisory on Haloperidol. This summary was updated by ECRI Institute on January 10, 2008 following the FDA advisory on Carbamazepine. This summary was updated by ECRI Institute on May 1, 2009 following the FDA advisory on antiepileptic drugs. This summary was updated by ECRI Institute on January 8, 2010 following the FDA advisory on Valproate sodium. The information was reaffirmed by the guideline developer in 2007 and updated by ECRI Institute on March 29, 2010. This summary was updated by ECRI Institute on September 15, 2010 following the FDA advisory on Lamictal (lamotrigine). This summary was updated by ECRI Institute on April 13, 2011 following the FDA advisory on Topamax (topiramate). This summary was updated by ECRI Institute on September 12, 2011 following the FDA advisory on Celexa (citalopram hydrobromide). This

summary was updated by ECRI Institute on April 16, 2012 following the updated FDA advisory on Celexa (citalopram hydrobromide). This summary was updated again by ECRI Institute on December 1, 2015. The updated information was not verified by the guideline developer. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines. This summary was updated by ECRI Institute on February 15, 2017 following the U.S. Food and Drug Administration advisory on general anesthetic and sedation drugs.

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